



## Antiparasitics, Topical Therapeutic Class Review (TCR)

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July 13, 2015

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## FDA-APPROVED INDICATIONS

Drug	Manufacturer	FDA-Approved Indication(s)
<b>Prescription</b>		
benzyl alcohol (Ulesfia®) <sup>1</sup>	Zylera	Age 6 months and older: Treatment of head lice
crotamiton (Eurax®) <sup>2</sup>	Ranbaxy	Treatment of scabies Symptomatic treatment of pruritus
ivermectin (Sklice®) <sup>3</sup>	Sanofi Pasteur	Age 6 months and older: Treatment of head lice
lindane <sup>4</sup>	generic	Treatment of head lice and ova Treatment of crab lice and ova Treatment of scabies
malathion (Ovide®) <sup>5</sup>	generic, Taro	Age 6 years and older: Treatment of head lice and ova
permethrin 5% cream (Elimite™) <sup>6</sup>	generic, Prestium Pharma	Treatment of scabies
spinosad (Natroba®) <sup>7</sup>	generic, ParaPRO	Age 6 months and older: Treatment of head lice
<b>Over-The-Counter (OTC)</b>		
permethrin 1% lotion (Nix®) <sup>8</sup>	generic, Insight Pharma	Treatment of head lice Prophylaxis during head lice epidemic
pyrethrins/piperonyl butoxide (RID®) <sup>9</sup>	generic, Bayer	Treatment of head lice Treatment of body lice Treatment of crab lice

Lindane is reserved for patients who cannot tolerate other approved therapies or have failed treatment with other approved therapies.

## OVERVIEW

Head lice, or *Pediculus humanus capitis*, are a worldwide public health concern affecting persons of all ages and socioeconomic backgrounds. In the U.S., it is most common among children 3 to 11 years old and accounts for 6 to 12 million annual infestations.<sup>10,11</sup> Head lice infestations are not typically associated with morbidity, are not a sign of uncleanliness, and do not transmit systemic disease, although secondary methicillin-resistant *Staphylococcus aureus* (MRSA) or streptococcal infections may occur.<sup>12,13,14</sup> Pediculosis is a source of social stigma and embarrassment and can prevent children with nits from attending school where a “no nit” policy is in place.<sup>15</sup> Itching is the primary symptom of pediculosis which results from an allergic reaction to the saliva lice inject during feeding.

The primary mode of head lice transmission is direct head-to-head contact. Lice crawl using adapted claws; they do not jump, hop, or fly. Once off the host, head lice only survive 15 to 20 hours.<sup>16</sup> In the U.S., head lice affects all socioeconomic groups; there is less infestation among African-Americans than other races, possibly due to a lack of adaptation of the lice claws to grasp specific shape and width hair shafts; hair length is not a factor.<sup>17</sup>

Topical pediculicides, toxic to the louse central nervous system (CNS), are the initial treatment choice for treatment of head lice.<sup>18</sup> Safety is a concern with pediculicides, since the infestation itself presents

minimal risk to the host.<sup>19</sup> The 2015 American Academy of Pediatrics (AAP) Head Lice Guidelines and the 2015 AAP Red Book Report of the Committee on Infectious Diseases recommend topical OTC permethrin 1% or pyrethrins, which have good safety profiles, as first-line for head lice when resistance to these products is not suspected.<sup>20,21</sup> When resistance to these agents is confirmed or treatment fails, malathion (Ovide) can be used in children 2 years and older or benzyl alcohol (Ulesfia) can be used in children older than 6 months. Ivermectin (Sklice) and spinosad (Natroba) may be used as alternatives in these cases of resistance, but the cost of the preparations should be taken into account by the prescriber. Lindane is no longer recommended by the AAP due to concerns with neurotoxicity, rare severe seizures in children, low ovicidal activity, and worldwide reports of resistance.

In a 2012 policy statement on pesticide exposure in children, the AAP introduced recommendations to minimize pediatric pesticide exposure. The AAP advises against overuse of pediculicides and advocates proper application methods to reduce children's exposure. Among common pesticides on AAP's list include: permethrin, malathion, and lindane.<sup>22</sup>

The 2015 AAP guidelines recommend checking all household members for head lice. Those with live lice or nits within 1 centimeter of the scalp should be treated.<sup>23</sup> The AAP also considers it prudent to prophylactically treat bedmates even if no live lice are found. The AAP does not recommend the routine use of pediculicide sprays since the nits are unlikely to incubate and hatch at room temperature or survive off the scalp beyond 48 hours. Clothing, furniture, or carpeting that has come in contact with the infested person 24 to 48 hours prior to treatment may be washed.

For treatment for *Pediculosis pubis*, or crab lice, the 2015 Centers for Disease Control and Prevention (CDC) Sexually Transmitted Diseases Treatment Guidelines recommend permethrin 1% cream or pyrethrins with piperonyl butoxide (RID) as first-line despite growing resistance.<sup>24</sup> Malathion or oral ivermectin (Stromectol) are considered alternative regimens. Lindane is second-line due to toxicity. According to the 2015 AAP Red Book report, pediculicides used to treat other kinds of louse infestations are effective for treatment of *Pediculosis pubis*.<sup>25</sup> However, topical pediculicides should not be used for treatment of crab lice infestation of eyelashes. All sexual contacts should be treated at the same time to prevent cross reinfection.

Causes of treatment failure in pediculosis or scabies include misdiagnosis, noncompliance, reinfestation, resistance, inadequate treatment, and lack of drug ovicidal or residual killing properties. Incorrect pediculicide application should be considered first when there is treatment failure. No currently available pediculicide is 100% ovicidal; resistance to permethrin, lindane, pyrethrins, and the United Kingdom formulation of malathion has been reported.<sup>26,27,28,29,30,31,32,33,34</sup> However, the actual rates of resistance to specific products can vary by region and are not fully known. Although presence of knockdown-type resistance alleles (*kdr* type) mutations alone may not predict clinical failure, their increasing frequency in head louse populations coincides with reports of product failure in controlled trials. A recent study of knockdown-type resistance alleles (*kdr* type) frequency in North American human head louse showed *kdr* type T917I (TI) increased to 99.6% (from 2007 to 2009) in the U.S., whereas it was 88.4% (from 1999-2009).<sup>35</sup> This increase in resistance is attributed to the extensive use of pyrethrin and permethrin-based pediculicides over many years. Benzyl alcohol (Ulesfia) resistance is unlikely due to its mechanism of action, but as its therapeutic effects are directed at the louse and not the ovum, a full treatment course involves reapplication after 7 days to ensure eradication of hatched ova.<sup>36,37</sup> Treatment failure should be suspected if live lice are still present 2 to 3 days after the second

treatment of a product has been applied correctly, and no other cause of failure can be identified. Subsequent treatment should be with a different class.<sup>38,39</sup> Using higher strengths of permethrin are not more efficacious.<sup>40,41</sup>

According to the 2015 AAP Red Book report, treatment of *Pediculosis Corporis* (body lice) consists of improving hygiene and regular changes of clean clothes and bedding.<sup>42</sup> Infested clothing can be decontaminated by washing in hot water (at least 130° F), by machine drying at hot temperatures, by dry cleaning, or by pressing with a hot iron. Pediculicides typically are not needed if materials are laundered at least weekly. However some people with significant body hair may require full-body treatment with a pediculicide, as lice and eggs may adhere to body hair.

Scabies is a major public health concern in many poor regions. Scabies is caused by an 8-legged obligate human parasitic mite *Sarcoptes scabiei* and results in intense pruritus which is due to a delayed type-IV hypersensitivity reaction to the mite, its feces, and eggs. There is also a characteristic rash and distribution pattern. It can affect the entire body but, in adults, the head and neck are usually not affected. The female mite burrows under the skin and lays 10 to 25 eggs before dying. The eggs hatch in 3 days, leave the burrow for the skin surface, and mature into adults. Scabies can cause morbidity from secondary infections. If left untreated, staphylococcal infections including impetigo, ecthyma, paronychia, and furunculosis can occur.<sup>43,44</sup> Transmission of scabies is usually from direct person-to-person contact. The mites can survive off a host for 24 to 36 hours and longer in colder temperatures.<sup>45,46</sup> Crusted scabies or Norwegian scabies, an aggressive form of scabies, can occur in immunocompromised patients.

The 2015 CDC Sexually Transmitted Diseases (STD) Treatment Guidelines and the 2015 AAP Red Book Report of the Committee on Infectious Diseases recommend topical permethrin 5% or oral ivermectin as first-line for the treatment of scabies, despite resistance to permethrin.<sup>47,48</sup> The CDC recommends lindane only as a second-line due to associated CNS toxicity and resistance. Because of safety concerns and availability of other treatments, the 2015 AAP Red Book report does not recommend lindane for scabies treatment.<sup>49</sup> Crotamiton (Eurax) is not mentioned in the CDC guidelines; however, it does have a role as an antipruritic in scabies.<sup>50</sup> All family members and close contacts must be prophylactically treated at the same time. Unlike head lice, environmental measures are essential for successful treatment of scabies, since mites can survive off the host. Clothes, linens, and towels must be washed with hot water and heat dried, dry-cleaned, or placed in a sealed plastic bag for at least 72 hours.

Systemic agents are used in the treatment of head lice, crab lice, and scabies, particularly in resistant cases. This review focuses on the available prescription topical antiparasitic treatments for head lice, crab lice, and scabies.

## PHARMACOLOGY<sup>51, 52, 53, 54, 55, 56, 57</sup>

The exact mechanism of crotamiton (Eurax) is not known. It has scabicial activity against *Propionibacterium acnes* and *S. scabiei*, as well as antipruritic actions.

Benzyl alcohol (Ulesfia) is a topical pediculicide. It inhibits lice from closing their respiratory spiracles, which results in obstruction of the spiracles by the vehicle and subsequent asphyxiation of the lice. Benzyl alcohol does not have ovicidal activity; therefore, therapy must be repeated after 7 days.

Ivermectin (Sklice) is a member of the avermectin class and works primarily by binding selectively and with high affinity to glutamate-gated chloride channels. This leads to an increase in permeability of the cell membrane to chloride ions with hyperpolarization of the nerve or muscle cell, and results in paralysis and death of the parasite. Avermectin selectivity is attributed to some mammals not having glutamate-gated chloride channels and the avermectins have a low affinity for mammalian ligand-gated chloride channels. In humans, ivermectin does not cross the blood-brain barrier.

Lindane is directly absorbed by parasites and their ova. It non-competitively inhibits gamma amino butyric acid (GABA) receptors. Lindane stimulates the nervous system, resulting in seizures and death of the parasites. Lindane resistance is thought to be via the GABA receptor becoming less sensitive to GABA antagonists.

Malathion (Ovide) is an organophosphate which acts as a pediculicide by inhibiting cholinesterase activity *in vivo*. Malathion resistance is thought to occur by increased levels of carboxylesterases that are involved in the drugs metabolism into non-malaxon intermediates.

Permethrin (Elimite) is a synthetic pyrethroid which inhibits sodium ion influx through nerve cell membrane channels in ectoparasites, resulting in delayed repolarization and resultant paralysis and death of the parasites. Pyrethroid resistance is mediated by mutation of the alpha subunit gene of the neuronal voltage-gated sodium channel, conferring decreased sensitivity of the channel to pyrethroids. This is referred to as knock-down resistance. Spinosad (Natroba) is a topical pediculicide that works by neuronal excitation in insects causing lice to become paralyzed and die. Although nit removal is not required, spinosad should be used in the context of an overall lice management program.

None of the pediculicides are 100% ovicidal.

## PHARMACOKINETICS<sup>58,59,60,61,62,63,64</sup>

Benzyl alcohol (Ulesfia) has shown systemic concentrations ranging from 1.97 to 2.99 mcg/mL 30 minutes post treatment and 1.63 mcg/mL 1 hour after treatment.

The degree of systemic absorption following topical administration of crotamiton (Eurax) or malathion (Ovide) has not been determined, although the potential exists.

In a small pharmacokinetic study of 20 subjects ranging from 6 months to 3 years of age, after single application ivermectin (Sklice), the mean plasma concentration and area under the concentration-time curve from zero to time of last measurable concentration were 0.24 plus or minus 0.23ng/mL and 6.7 plus or minus 11.2hr ng/mL, respectively.

Lindane lotion and shampoo have shown a systemic absorption of up to 10%. Lindane is rapidly distributed followed by a longer beta-elimination phase. It is metabolized hepatically, excreted in the

urine and feces, and has 4 major primary and 2 major secondary metabolites. Its half-life is about 18 hours.

Permethrin has a systemic absorption of 2% or less. It is metabolized by ester hydrolysis in the liver to inactive metabolites and is excreted primarily in the urine.

In a small pharmacokinetic study, spinosad (Natroba) plasma levels were below the level of quantitation in all samples from 14 children.

## CONTRAINDICATIONS/WARNINGS<sup>65,66,67,68,69,70,71</sup>

Lindane is contraindicated in uncontrolled seizure disorders, crusted (Norwegian) scabies, or any condition which may increase systemic absorption. It is also contraindicated in premature infants. Lindane carries a boxed warning as its use may be associated with severe neurologic toxicities. Caution should be exercised in patients weighing less than 50 kg, particularly in infants, children, elderly, or patients with history of seizures, conditions which may increase risk of seizures, or taking medications which may lower the seizure threshold.

Malathion (Ovide) is contraindicated in neonates and infants. Malathion labeling advises of the potential for second-degree chemical burns and stinging. Malathion lotion is flammable; avoidance of heat sources, including open flames and lighted cigarettes, is required.

Benzyl alcohol (Ulesfia) and spinosad (Natroba) should not be used in patients less than 6 months old. Neonates (less than 1 month old or preterm infants with a corrected age of less than 44 weeks) can be at risk for gasping syndrome if treated with benzyl alcohol lotion. Intravenous (IV) administration of products containing benzyl alcohol has been associated with neonatal gasping syndrome consisting of severe metabolic acidosis, gasping respirations, progressive hypotension, seizures, CNS depression, intraventricular hemorrhage, and death in preterm, low birth weight infants.

Permethrin (Elimite) is contraindicated in infants less than 2 months old. Treatment with permethrin may temporarily exacerbate symptoms of itching, redness, and swelling. Itching may occur even after successful killing of lice. Rare cases of asthma exacerbations have been reported with use of pyrethroid-based products, such as permethrin in patients with ragweed or chrysanthemum allergies.<sup>72</sup>

Ivermectin (Sklice) should not be used in patients less than 6 months of age. It should only be administered under adult supervision as accidental ingestion may occur in pediatric patients.

These agents are for external use only. Contact with face, eyes, and mucous membranes should be avoided. Acutely inflamed or raw skin should also not come into contact with these products.

Avoid fire, flame, smoking, and electric heat sources for hair (e.g., hair dryers) following use of malathion; it contains 78% isopropyl alcohol and is highly flammable.

## DRUG INTERACTIONS<sup>73,74,75,76,77,78,79</sup>

No drug interactions have been reported for crotamiton (Eurax), ivermectin (Sklice), malathion (Ovide) permethrin (Elimite), or spinosad (Natroba). Increased toxicity has been reported with the use of lindane and drugs which can lower seizure threshold. Oils, creams, or ointments may enhance lindane absorption; concomitant use should be avoided. Drug interaction studies were not conducted for benzyl alcohol (Ulesfia).

## ADVERSE EFFECTS<sup>80,81,82,83,84,85</sup>

Drug	Dermatitis	Pruritus/ Rash	Burning/ Stinging	Paresthesia	Erythema	Headache	Seizures
benzyl alcohol (Ulesfia)*	<1	12 (pruritus) <1 (rash)	<1	<1**	10	nr	nr***
crotamiton (Eurax)	reported	reported	nr	nr	nr	nr	nr
ivermectin (Sklice)****	<1	nr	<1	nr	nr	nr	nr
lindane	reported	reported	nr	reported	nr	reported	reported
malathion (Ovide)	reported	nr	reported	nr	nr	nr	nr
permethrin (Elimite)	nr	7 (pruritus) ≤ 2 (rash)	10	≤ 2	≤ 2	reported	nr
spinosad (Natroba)	nr	nr	nr	nr	3	nr	nr**

Adverse effects data are reported as percentages. Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive. nr = not reported

\* Pyoderma and ocular irritation were reported in 7% and 6% of patients taking benzyl alcohol, respectively.

\*\* Application site anesthesia and hypoesthesia were reported in 2% of patients using benzyl alcohol, respectively.

\*\*\* IV products containing benzyl alcohol have been associated with neonatal gasping syndrome characterized by a number of symptoms including seizures.

\*\*\*\* Conjunctivitis, ocular hyperemia, and eye irritation were reported in less than 1% of patients taking ivermectin.

## SPECIAL POPULATIONS<sup>86, 87, 88, 89, 90, 91, 92</sup>

### Pediatrics

Safety and effectiveness of benzyl alcohol (Ulesfia) have not been established in patients less than 6 months old.

Safety and effectiveness of ivermectin (Sklice) have not been established in patients less than 6 months old. There is potential for increased systemic absorption due to a high ratio of skin surface area to body mass and the potential for immature skin barrier and risk of ivermectin toxicity.

Pyrethrin/piperonyl butoxide topicals should not be used in children less than 2 years old.

Safety and effectiveness of crotamiton (Eurax) have not been established in pediatrics.

Extreme caution should be exercised for lindane in patients who weigh less than 50 kg, particularly in infants and children. Lindane is contraindicated in premature infants.

Safety and effectiveness of malathion (Ovide) have not been established in pediatrics younger than 6 years old; its use is contraindicated in neonates and infants.

Safety and effectiveness of OTC and prescription permethrin have not been established in patients less than 2 months old.

The safety and effectiveness of spinosad (Natroba) in patients less than **6 months** of age have not been established.



## Pregnancy

Crotamiton, ivermectin, and lindane are classified as Pregnancy Category C. Benzyl alcohol, malathion, permethrin and spinosad are Pregnancy Category B.

## Hepatic Impairment

Lindane must be used with caution in patients with hepatic impairment.

## Geriatrics

The safety of benzyl alcohol has not been established in patients over 60 years old.

Clinical studies with crotamiton did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently than younger subjects. Other reported clinical experience has not identified differences in responses between these patient groups, but greater sensitivity of some older individuals cannot be ruled out.

## DOSAGES<sup>93,94,95,96,97,98,99,100</sup>

Drug	Instructions	Availability
<b>Prescription</b>		
benzyl alcohol (Ulesfia)	Lice: Apply to dry hair and scalp; Rinse after 10 minutes; Repeat treatment in 7 days; Usage guideline is based on hair length	5% lotion
crotamiton (Eurax)	Scabies: Thoroughly massage into the skin of the whole body from the chin down, paying particular attention to all folds and creases; Repeat in 24 hours; A cleansing bath should be taken 48 hours after final application Pruritus: Apply to affected areas as directed; repeat as needed	10% cream, lotion
ivermectin (Sklice)	Lice: Apply to dry hair and scalp in an amount up to 1 tube to thoroughly coat hair and scalp; Rinse after 10 minutes with water; Do not retreat (for single application only)	0.5% lotion
lindane	Lice: Apply <u>shampoo</u> once to hair as directed; Do not retreat Scabies: Apply <u>lotion</u> once from neck to toes as directed; Rinse after 8 to 12 hours; Do not retreat	1% lotion 1% shampoo
malathion (Ovide)	Lice: Apply once to dry hair as directed; Rinse after 8 to 12 hours; Repeat in 7 to 9 days if needed	0.5% lotion
permethrin (Elimite)	Scabies: Apply once from head to toe; Rinse after 8 to 14 hours as directed; Repeat in 14 days if live mites are present	5% cream
spinosad (Natroba)	Lice: Apply to cover dry scalp, then apply to dry hair; Depending on hair length, apply up to 120 mL (1 bottle) to adequately cover scalp and hair; Leave on for 10 minutes, then thoroughly rinse off spinosad with warm water; If live lice are seen 7 days after the first treatment, a second treatment should be applied	0.9% suspension



### ***Dosages (continued)***

Drug	Instructions	Availability
<b>OTC</b>		
permethrin (Nix)	Lice treatment: Apply to hair and scalp as directed; Rinse after 10 minutes; If live lice are seen 7 days or more after the first application, a second treatment should be given Lice prophylaxis: Apply to hair and scalp as directed; Rinse after 10 minutes; In epidemic settings, a second prophylactic application is recommended 2 weeks after the first application	1% lotion/1% cream rinse
pyrethrins/piperonyl butoxide (RID)	Lice: Apply to dry hair and scalp or skin as directed; Rinse after 10 minutes; Repeat application once in 7 to 10 days Body Lice and Crab Lice: Apply liberally to skin as directed; Rinse after 10 minutes; Repeat application once in 7 to 10 days	0.33%/4% shampoo, topical foam

Previous recommendations have instructed patients to re-treat in 7 to 10 days with pyrethrins; however, some evidence based on the life cycle of lice suggests that re-treatment at day 9 is optimal. An alternate schedule of 3 treatments with non-ovicidal products on days 0, 7, and 13 to 15 has been proposed.<sup>101</sup>

Before application of crotamiton, the affected skin should be thoroughly washed and loose scales scrubbed, rinsed, and towel dried.

Lindane shampoo should be applied to dry hair and massaged for 4 minutes; water is added gradually to create lather. Most patients will require 1 ounce of shampoo. Some patients may require 2 ounces of shampoo based on length and density of hair.

Nit combing is not required with spinosad but may assist with removal.<sup>102</sup>

Most patients with scabies will require 1 ounce of permethrin 5% cream.

These agents require application to the head, base of the neck, and behind the ears.

## **CLINICAL TRIALS**

### **Search Strategy**

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class, pediculosis capitis, pediculosis pubis, and scabies. Randomized controlled comparative trials for FDA-approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

There are few well-designed studies for head lice; a number of the studies compare the topical agents to agents outside of this review, so they were not included. There are also few well-designed studies for scabies. A number of the studies compare the topical agents to oral therapy, so they were not included. There were no acceptable studies found for crab lice. Due to the lack of acceptable data, this evaluation includes studies performed versus permethrin 1% OTC (Nix), a lower strength than the prescription product included in this review. Open-label and pooled data were determined to be unacceptable. Many studies use the investigator-blinded design rather than using the double-blinded method and were included. Only placebo-controlled trials are available for benzyl alcohol (Ulesfia) and ivermectin (Ulesfia) and are included.

## Head Lice

### ***malathion (Ovide) and permethrin (Nix)***

A randomized, investigator-blinded study of 66 children, mean age of 11.4 years old, with head lice compared malathion 0.5% lotion to permethrin 1% creme rinse.<sup>103</sup> Both agents were applied according to label instructions, except malathion was applied for a reduced time of 20 minutes instead of the approved label of 8 to 12 hours. At day 8, patients still with live lice were retreated with the same agent they were initially treated with on day 1. Ovicidal and pediculicidal efficacy were evaluated on days 8 and 15. Treatment success was defined as being free of lice and viable eggs at day 15. Malathion was 98% pediculicidal and ovicidal versus 55% for permethrin at day 15 ( $p<0.0001$ ). At day 8, 50% less malathion patients required treatment versus the permethrin group. The reinfestation rate for malathion versus permethrin was 0% versus 33%, respectively.

### ***malathion gel, malathion (Ovide) and permethrin (Nix)***

A randomized, investigator-blinded, parallel-group, active-controlled study of 172 patients with head lice compared malathion 0.5% gel (30-, 60-, 90-minute applications), malathion 0.5% lotion (8- to 12-hour applications), and permethrin 1% creme rinse.<sup>104</sup> Patients were treated on day 1 and re-evaluated on day 8; retreatment was done with the same product as given on day 1 if live lice were present. Cure was defined as absence of live lice on day 14. Using intention-to-treat, treatment success rates were 98% for the 30-minute malathion gel ( $p<0.0001$ ), 97% for malathion lotion ( $p=0.006$ ), and 45% for permethrin. Retreatment was highest for permethrin at 70%. Adverse events between treatment groups were not significantly different. Malathion gel is not commercially available in the U.S.

### ***permethrin (Nix) and lindane***

A randomized, single-blinded, multicenter study of 573 patients with head lice compared efficacy and tolerance of permethrin creme rinse 1% and lindane 1% shampoo.<sup>105</sup> Both were applied according to the label: permethrin for 10 minutes and lindane for 4 minutes. At 14 days, 99% in the permethrin group were lice-free versus 85% of patients on lindane. This was statistically significant. Adverse events were mild and difficult to distinguish from infestation symptoms.

### ***benzyl alcohol (Ulesfia) and placebo***

Two randomized, double-blind, vehicle-controlled, multicenter studies evaluated benzyl alcohol 5% lotion in 628 patients 6 months of age and older with active head lice infestation.<sup>106</sup> Treatment was applied 2 times (10 minutes each) separated by 1 week. Efficacy was assessed as the proportion of subjects who were free of lice 14 days after the final treatment. For evaluation of efficacy, the youngest subject from each household was enrolled in the Primary Treatment Cohort. Other infested household members were enrolled in a Secondary Treatment Cohort and received the same treatment as the youngest subjects. This Secondary Treatment Cohort was not included in the efficacy analysis but was evaluated for safety. Both study 1 and study 2 randomized 125 Primary Treatment Cohort subjects each. Fourteen days after the last treatment, both studies combined showed that 75% of the subjects treated with benzyl alcohol topical lotion were lice free, compared with 15% in the vehicle groups.

### ***ivermectin (Sklice) and placebo***

Two randomized, double-blind, vehicle-controlled, multicenter studies were conducted in patients 6 months of age and older with head lice infestation.<sup>107,108</sup> All patients received a single 10 minute application of either ivermectin lotion or vehicle control with instructions not to use a nit comb. For the evaluation of efficacy, the youngest subject from each household was considered to be the primary subject of the household (n=289), and other members in the household were enrolled in the study as secondary subjects, and evaluated for all safety parameters. The primary efficacy was assessed as the proportion of index subjects who were free of live lice at day 2 and through day 8 to the final evaluation 14 (plus or minus 2 days) following a single application. Proportion of subjects who were free of live lice 14 days after the final treatment in the first study was 16.2% versus 76.1% for vehicle versus ivermectin lotion. This efficacy measurement in the second study was 18.9% versus 71.4% for vehicle versus ivermectin lotion. Adverse reactions, reported in less than 1% of subjects treated with ivermectin include conjunctivitis, ocular hyperemia, eye irritation, dandruff, dry skin, and skin burning sensation.

### ***ivermectin (Sklice) and placebo***

A randomized, blinded study was conducted in 78 patients aged 2 to 62 years to investigate the effectiveness of 3 ivermectin lotion concentrations (0.15%, 0.25%, and 0.5%) compared with vehicle placebo in the treatment of head lice.<sup>109</sup> The subjects received a single 10 minute application of product on day 1. Evaluations were completed at 2 and 6 hours post-application, and on days 2, 8 ( $\pm 1$ ), and 15 ( $\pm 2$ ). Compared with placebo, all ivermectin concentrations resulted in the statistically significant ( $p \leq 0.003$ ) eradication of head lice through to day 15, with the highest level of eradication (73.7%) in subjects who received the 0.5% concentration. The severity of pruritus decreased from baseline in all treatment groups, including the placebo group, from 6 hours post-treatment to day 15, with the greatest reduction in the 0.5% concentration group. No ocular irritation was observed. All 3 ivermectin treatment strengths and vehicle were well tolerated.

### ***spinosad (Natroba) and permethrin (Nix)***

Two multicenter, randomized, investigator-blind, active-controlled studies (n=1,038) were conducted in patients 6 months of age and older with head lice infestation.<sup>110,111</sup> Patients were randomized to spinosad 0.9% topical crème rinse or permethrin 1% crème rinse. For the evaluation of efficacy, the youngest subject from each household was considered to be the primary subject of the household, and other members in the household were enrolled in the study as secondary subjects, and evaluated for all safety parameters.

All patients who were treated on day 0 returned for efficacy evaluation at day 7. If live lice were present at day 7, they received a second treatment. Patients who were lice free on day 7 returned on day 14 for evaluation. Patients with live lice and who received a second treatment returned on days 14 and 21. Proportion of primary subjects who were free of live lice 14 days after the final treatment in the first study was 84.6% versus 44.9% for spinosad versus permethrin (p<0.001). This efficacy measurement in the second study was 86.7% versus 42.9% for spinosad versus permethrin (p<0.001). Few adverse events were reported, and were mild to moderate, including eye irritation (permethrin), ocular hyperemia, and application-site erythema/irritation (both medications).

## **Scabies**

### ***permethrin and lindane***

A randomized, investigator-blinded, multicenter study compared the safety and efficacy of a single, whole-body application of permethrin 5% cream to lindane 1% lotion in 467 patients with scabies.<sup>112</sup> After 28 days of application, complete resolution was similar in permethrin and lindane groups (91% and 86%, respectively). Patients had pruritus secondary to scabies in 14% of permethrin and 25% of lindane groups. New or increased pruritus and mild, transient burning were the most common adverse events and occurred slightly more often in the permethrin group.

### ***permethrin (Elimite) and crotamiton (Eurax)***

Permethrin 5% cream was compared for effectiveness to crotamiton 10% cream for the treatment of scabies in a randomized, double-blinded study of 47 children between the ages of 2 months and 5 years.<sup>113</sup> Permethrin cured 30% of children versus 13% for crotamiton after 14 days. Four weeks after treatment, cure rates were 89% and 60%, respectively.

### ***permethrin, lindane, and crotamiton (Eurax)***

A randomized, parallel-group study of 150 patients with scabies compared permethrin 5% to lindane 1% and crotamiton 10%.<sup>114</sup> Patients were treated for 2 consecutive nights from neck to toe and then examined at various times for up to 4 weeks after the last treatment. Cure, defined as no new lesions and eradication of all original lesions, occurred in 98% of patients treated with permethrin, 88% of patients treated with crotamiton, and 84% treated with lindane. Cure rate was also highest among patients less than 10 years old with permethrin (100%) compared to crotamiton (80%) or lindane (zero%). No adverse events were reported in any of the treatment groups.

## **META-ANALYSES**

A Cochrane review of randomized trials of pediculicides found permethrin, synergized pyrethrin, and malathion effective in the treatment of lice.<sup>115</sup> The review found no evidence that any 1 pediculicide

has greater effect than another. However, the emergence of resistance since these trials were conducted means there is no direct contemporary evidence of the comparative effectiveness of these products. The review emphasizes that the choice of therapy is dependant on local resistance patterns. The review also included studies utilizing physical methods and found them to be ineffective in treating head lice. Comparative studies with agents in this class support this finding.<sup>116, 117</sup> Adverse events reported were minor; however, the reporting quality varied among trials.

A Cochrane review of randomized trials of topical and systemic treatments for scabies found 20 small trials involving 2,392 patients.<sup>118</sup> Permethrin was more effective than oral ivermectin, crotamiton, and lindane. Permethrin also appeared more effective in reduction of itch persistence than either crotamiton or lindane.

## SUMMARY

AAP Guidelines from 2015 and the 2015 Red Book report continue to support a role for topical OTC permethrin and pyrethrins in the treatment of head lice, but resistance to these agents has been documented in the U.S. A recent study of knockdown-type resistance alleles (kdr type) shows an increased frequency of 99.6% resistance to human head louse in the U.S. This increase is attributed to widespread use of pyrethrin and permethrin-based pediculicides. Higher concentrations of permethrin or longer application times for the same agent kill few additional lice. Newer agents may have a role when resistance to permethrin or pyrethrins is a concern or in treatment failure. For treatment failures not attributable to improper use of an over-the counter pediculicide, malathion, benzyl alcohol lotion, or spinosad suspension should be used. Selection of agents should be made based on safety, efficacy, local resistance patterns, and patient age.

Caution should be used with malathion in order to prevent serious adverse events due to its high alcohol content; chemical burns with this agent have been reported. Lindane is no longer recommended for the treatment of head lice due to its poor safety and efficacy.

Benzoyl alcohol (Ulesfia) has not been compared to other agents but has shown efficacy in head lice. Spinosad (Natroba) has shown better head lice eradication compared to topical permethrin but has not been compared to other prescription topical antiparasitics. Similar to benzyl alcohol (Ulesfia) topical lotion, spinosad topical suspension contains benzyl alcohol, which is associated with neonatal gasping syndrome. Spinosad is approved for use in patients **6 months** of age and older.

Ivermectin (Sklice) is a topical antiparasitic agent approved for patients 6 months of age and older. Studies revealed that ivermectin (Sklice) has better head lice eradication compared to placebo, but comparison to other prescription topical antiparasitics is not currently available.

In the treatment of scabies, prescription permethrin is the recommended topical agent.

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